Listing of the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

1. (Currently amended) A method of identifying a mammalian protease mutein which cleaves a substrate sequence in a target protein involved with a pathology in a mammal, wherein the target protein is selected from the group consisting of a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor, and a signaling protein that regulates apoptosis, and wherein cleavage of said substrate sequence in said target protein serves as a treatment for said pathology, the method comprising the steps of:

   (a) producing a library of mutein protease sequences, each different mutein protease sequence in the library being a member of the library, each member having N mutations relative to a wild-type scaffold sequence of a ~~said~~ mammalian protease wherein N is a positive integer,

   (b) measuring ~~the~~ an activity of at least two members of the library in cleaving the substrate sequence, and

   (c) identifying at least one mutein protease having an increased cleavage activity and/or altered specificity for cleaving said substrate sequence, relative to the wild-type scaffold sequence.

2. (Original) The method of claim 1, wherein the protease is a serine or cysteine protease.

3. (Previously presented) The method of claim 1, wherein N is an integer between 1 and 20.

4. (Previously presented) The method of claim 3, wherein N is an integer from 1-5.

5. (Previously presented) The method of claim 3, wherein N is an integer from 5-10.

6. (Previously presented) The method of claim 3, wherein N is an integer from 10-20.

7. (Currently amended) The method of claim 1, wherein the mammalian protease scaffold has ~~the~~ an amino acid sequence derived from ~~of~~ one of the ~~members~~ proteases selected from ~~of~~ the group consisting of trypsin, chymotrypsin, subtilisin, ~~thrombin, plasmin, Factor Xa, uPA, tPA~~, MTSP-1, granzyme A, granzyme B, and granzyme M, elastase, chymase, papain, neutrophil elastase, ~~plasma kallikrein, urokinase type plasminogen activator,~~ complement factor serine proteases, ADAMTS13, neural endopeptidase/neprilysin, furin, and cruzain.

8. (Canceled)

9. (Currently amended) The method of claim ~~8~~ 1, wherein the pathology is ~~a member of~~ selected from the group consisting of rheumatoid arthritis, sepsis, cancer, acquired immunodeficiency syndrome, respiratory tract infections, influenza, cardiovascular disease, and asthma.

10. (Canceled)

11. (Original) The method of claim 1, wherein the target protein is involved in apoptosis.

12. (Currently amended) The method of claim ~~11~~ 9, wherein the target protein is caspase-3, VEGF or VEGF-R.

13. (Currently amended) The method of claim 1, wherein the ~~specific activity~~ specificity of the ~~detected~~ identified protease mutein for cleaving the substrate sequence is increased by at least 10-fold compared to the ~~activity~~ specificity of the wild-type scaffold sequence for cleaving that substrate sequence.

14. (Currently amended) The method of claim 1, wherein the ~~specific activity~~ specificity of the ~~detected~~ identified protease mutein for cleaving the substrate sequence is increased by

at least 100-fold compared to the ~~activity~~ specificity of the wild-type scaffold sequence for cleaving that substrate sequence.

15. (Currently amended) The method of claim 1, wherein the ~~specific activity~~ specificity of the ~~detected~~ identified ~~mutein~~ protease mutein for cleaving the substrate sequence is increased by at least 1000-fold compared to the ~~activity~~ specificity of the wild-type scaffold sequence for cleaving that substrate sequence.

16. (Currently amended) The method of claim 1, further comprising the steps of:

(d) providing two or more members of the protease library identified with increased cleavage activity and/or altered specificity,

(e) combining the mutations on a first ~~scaffold~~ mutein protease with the mutations on a second ~~scaffold~~ mutein protease to produce a third ~~scaffold~~ mutein protease; and

(f) identifying whether the combination produces a combined specificity protease that has increased cleavage activity and/or altered specificity in regards to the substrate sequence.

17-44. (Canceled)

45. (Currently amended) The method of claim 1, wherein the steps are repeated iteratively to create a variant protease ~~comprising the~~ having a desired specificity, activity and selectivity.

46. (Currently amended) The method of claim 45, further comprising comparing the ~~activity~~ specificity of the identified mutein protease against a mutein protease identified in an earlier iteration of the method, and identifying the mutein protease having increased ~~activity~~ efficiency of cleavage of the substrate sequence.

47. (Currently amended) The method of claim 1, further comprising comparing the ~~activity~~ specificity of the identified mutein protease against its corresponding wild type protease.

48. (Previously presented) The method of claim 1, wherein the substrate sequence is a sequence in a human protein.

49. (Canceled)

50. (Previously presented) The method of claim 1, further comprising the steps of providing at least one mutein protease identified in step (c), and testing the mutein protease in a cell-based assay against a target protein comprising the substrate sequence.

51. (Currently amended) The method of claim 50, wherein the member of the library identified in step (~~d~~ c) has the highest measured cleavage activity.

52. (Currently amended) The method of claim ~~50~~ 1, further comprising the steps of providing at least one mutein protease identified in step (c), and testing the mutein protease in~~, wherein the cell-based assay is~~ an *in vivo* assay.

53. (Currently amended) A method of identifying a mammalian protease mutein which cleaves a substrate sequence in a target protein involved with a pathology in a mammal, wherein cleavage of said sequence in said target protein serves as a treatment for said pathology, wherein the mammalian protease is selected from the group consisting of granzyme A, granzyme B, granzyme M, cathepsin, trypsin, chymotrypsin, subtilisin, MTSP-1, elastase, chymase, tryptase, chymotrypsin, collagenase, papain, neutrophil elastase, complement factor serine proteases, ADAMTS13, neural endopeptidase/neprilysin, furin, and cruzain, the method comprising the steps of:

(a) producing a library of ~~mutein~~ protease mutein sequences, each different ~~mutein~~ protease mutein sequence in the library being a member of the library, each member having N mutations relative to a wild-type scaffold sequence of said mammalian protease, wherein N is a positive integer;

(b) measuring ~~the~~ an activity of at least two members of the library in cleaving the substrate sequence;

(c) identifying at least one ~~mutein~~ protease mutein having a measured increase in cleavage activity and/or altered specificity for cleaving said substrate sequence relative to the wild type scaffold sequence;

(d) providing two or more members of the protease mutein library identified with increased cleavage activity and/or altered specificity for cleaving said substrate sequence;

(e) combining ~~the~~ mutations ~~on~~ in a first ~~scaffold~~ mutein with increased cleavage activity with ~~the~~ mutations ~~on~~ in a second ~~scaffold~~ mutein ~~with increased cleavage activity~~ to produce a third ~~scaffold~~ mutein;

(f) identifying whether the ~~combination~~ third mutein produces a ~~combined specificity~~ protease that has increased cleavage activity toward the substrate sequence and/or altered specificity for cleaving said substrate sequence~~; and~~

~~(g) comparing the activity of the test third mutein against said mammalian proteasethe wild type scaffold, or some other reference sequence, or to an earlier version a mutein identified during an iterative process of incrementally selecting for increasing activity~~.

54. (Currently amended) The method of claim 53, the method further comprising the steps of:

(~~h~~g) providing at least one ~~mutein~~ protease mutein identified in step (c); and

(~~i~~j) testing the ~~mutein~~ protease mutein in a cell-based assay against a target protein comprising the substrate sequence.

55. (Canceled)

56. (Previously presented) The method of claim 53, wherein the cell-based assay is an *in vivo* assay.

57. (Currently amended) The method of claim 53, wherein the steps are repeated iteratively to create a variant protease ~~comprising the~~ having a desired specificity and selectivity.

58. (Previously presented) The method of claim 53, wherein the substrate sequence is a sequence in a human protein.

59. (New) A method of identifying a human protease mutein which cleaves a substrate sequence in a target protein involved with a pathology in a human, wherein cleavage of said sequence in said target protein serves as a treatment for said pathology, wherein the target protein is selected from the group consisting of a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor, and a signaling protein that regulates apoptosis, the method comprising the steps of:

(a) producing a library of protease mutein sequences, each different protease mutein sequence in the library being a member of the library, each member having N mutations relative to a wild-type scaffold sequence of said mammalian protease, wherein N is a positive integer, wherein said protease is selected from the group consisting of granzyme A, granzyme B, granzyme M, cathepsin, trypsin, chymotrypsin, subtilisin, MTSP-1, elastase, chymase, tryptase, chymotrypsin, collagenase, papain, neutrophil elastase, complement factor serine proteases, ADAMTS13, neural endopeptidase/neprilysin, furin, and cruzain,

(b) measuring an activity of at least two members of the library in cleaving the substrate sequence, wherein said target protein is selected from the group consisting of a cell surface molecule that transmits an extracellular signal for cell proliferation, a cytokine, a cytokine receptor, and a signaling protein that regulates apoptosis, and

(c) identifying at least one protease mutein having an increased cleavage activity and/or altered substrate specificity for cleaving said substrate sequence, relative to the wild-type scaffold sequence.

60. (New) The method of claim 59, wherein step (c) is accomplished by identifying at least one protease mutein having altered substrate specificity for cleaving said substrate sequence, relative to the wild-type scaffold sequence.

61. (New) The method of claim 59, wherein the protease is Granzyme B or MTSP-1.

62. (New) The method of claim 59, wherein the target protein is selected from the group consisting of caspase 3, tumor necrosis factor, tumor necrosis factor receptor, interleukin-1, interleukin-1 receptor, interleukin-2, interleukin-2 receptor, interleukin-4, interleukin-4 receptor, interleukin-5, interleukin-5 receptor, interleukin-12, interleukin-12 receptor, interleukin-13, interleukin-13 receptor, p-selectin, p-selectin glycoprotein ligand, Substance P, Bradykinin, PSGL, factor IX, immunoglobulin E, immunoglobulin E receptor, CCR5, CXCR4, glycoprotein 120, glycoprotein 41, CD4, hemaglutinin, respiratory syncytium virus fusion protein, B7, CD28, CD2, CD3, CD4, CD40, vascular endothelial growth factor, VEGF receptor, fibroblast growth factor, endothelial growth factor, EGF receptor, TGF receptor, transforming growth factor, Her2, CCR1, CXCR3, CCR2, Src, Akt, Bcl-2, BCR-Abl, glucagon synthase kinase-3, cyclin dependent kinase-2 (cdk-2), and cyclin dependent kinase-4 (cdk-4).

63. (New) A method of identifying a human protease mutein which cleaves a substrate sequence in a target protein involved with a pathology in a mammal, wherein cleavage of said sequence in said target protein serves as a treatment for said pathology, the method comprising the steps of:

(a) producing a library of human protease mutein sequences, each different protease mutein sequence in the library being a member of the library, each member having N mutations relative to a wild-type scaffold sequence of a human protease wherein N is a positive integer, wherein said human protease is selected from the group consisting of granzyme A, granzyme B, granzyme M, cathepsin, MTSP-1, elastase, chymase, tryptase, chymotrypsin, collagenase, Factor Xa, Protein C, plasma kallikrein, plasmin, trypsin, thrombin, complement factor serine proteases, papain, ADAMTS13, endopeptidase, furin, cruzain and plasminogen activator,

(b) measuring an activity of at least two members of the library in cleaving the substrate sequence, wherein said target protein is selected from the group consisting of caspase 3, tumor necrosis factor, tumor necrosis factor receptor, interleukin-1, interleukin-1 receptor, interleukin-2, interleukin-2 receptor, interleukin-4, interleukin-4 receptor, interleukin-5, interleukin-5 receptor, interleukin-12, interleukin-12 receptor, interleukin-13, interleukin-13 receptor, p-selectin, p-selectin glycoprotein ligand,

Substance P, Bradykinin, PSGL, factor IX, immunoglobulin E, immunoglobulin E receptor, CCR5, CXCR4, glycoprotein 120, glycoprotein 41, CD4, hemaglutinin, respiratory syncytium virus fusion protein, B7, CD28, CD2, CD3, CD4, CD40, vascular endothelial growth factor, VEGF receptor, fibroblast growth factor, endothelial growth factor, EGF receptor, TGF receptor, transforming growth factor, Her2, CCR1, CXCR3, CCR2, Src, Akt, Bcl-2, BCR-Abl, glucagon synthase kinase-3, cyclin dependent kinase-2 (cdk-2), and cyclin dependent kinase-4 (cdk-4), and

(c) identifying at least one protease mutein having an increased cleavage activity and/or altered substrate specificity for cleaving said substrate sequence, relative to the wild-type scaffold sequence.

64. (New) The method of claim 63, wherein step (c) is accomplished by identifying at least one protease mutein having altered substrate specificity for cleaving said substrate sequence, relative to the wild-type scaffold sequence.

65. (New) The method of claim 63, wherein said protease is selected from the group consisting of granzyme A, granzyme B, granzyme M and MTSP-1.

66. (New) The method of any one of claims 63-65, wherein the target protein is selected from the group consisting of caspase 3, vascular endothelial growth factor and VEGF receptor.